UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
09/285,531	04/02/99	CHERNAJOVSKY	Y	KIR95-01A

HM12/0615

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1646	18

DATE MAILED: 06/15/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/285,531	Applicant(s) CHERNAJOVSKY ET AL.	
	Examiner Eileen B. O'Hara	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 March 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6,8,14-17 and 19-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6,8,14-17 and 19-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *14* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 30, 2001 has been entered.

2. Receipt of the Supplemental Information Disclosure Statement and is acknowledged, as is compliance with the sequence requirements.

Status of Claims

3. Claims 1-3, 6, 8, 14-17 and 19-37 are pending in the instant application. Claims 1, 14 and 15 have been amended and claims 27-37 have been added as requested by Applicant in Paper Number 15, filed March 30, 2001.

Claim Objections

4.1 The objection to claim 14 has been withdrawn in view of Applicants's Amendment.

4.2 Claims 16 and 31 are objected to because of the following informalities: the word "linker" at the end of each claim should be plural, since there are two linkers in the encoded by the DNA constructs. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 20-23 and 34-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a tumor necrosis factor related disease, does not reasonably provide enablement for preventing a tumor necrosis factor related disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 20-23 and 34-37 require a method of preventing a tumor necrosis factor related disease comprising administering a TNF-inhibiting amount of a receptor molecule of the instant application. However, the phrase "preventing a tumor necrosis factor related disease", given its broadest reasonable interpretation with the specification, requires that absolutely no cell, nor tissue, would present any symptom of a disorder after treatment with the chimeric TNF receptor polypeptides. There is no evidence, either in the specification nor in the prior art, that any method to date can accomplish this goal. The specification presents the results of cytotoxic tests in cells, however there is no support for the prevention of any disorder, as is required by the claims, and neither can such support be obtained through reasonable extrapolation of the data.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 19-23, 27, 29 and 33-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6.1 Claims 19-23 and 33-37 are indefinite because claims 19, 20, 33 and 34 encompass a method of treatment by administration to a **host**, and in the biological arts a host usually refers to a cell or organism that is transformed with recombinant DNA, or is an organism in or on which a parasite lives, or is a recipient for a transplanted tissue or organ. Replacing "host" with "subject" or "patient" would obviate this rejection.

6.2 Claim 27 is indefinite because of the phrase "wherein the **tumor necrosis is** of human origin", and claim 1, from which is depends, encompasses a receptor and not a disease. Replacing "tumor necrosis is" with "tumor necrosis **factor receptors are**" would obviate this rejection.

6.3 Claim 29 is indefinite because as written, it is not clear if the entire receptor molecule or just the polypeptide linker comprises SEQ ID NO: 2.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7.1 The rejection of claims 1-3, 6, 8, 14-17 and 19-26 are maintained, claim 14 and new claims 27-37 are added, under 35 U.S.C. 103(a) as being unpatentable over Wallach et al., U.S. Patent No. 5,478,925 or Wallach et al., EP 0 526 905.

The claims remain rejected for reasons cited in the previous office action, Paper No. 8, at pages 2-4. Applicants' traverse the rejection and argue that Wallach et al. prepared multimers of the soluble form of TNF-R using chemical cross-linking methods, did not prepare a fusion multimer and did not specify the sequences of the TNF monomers or the linker peptides.

Applicants' arguments have been considered but are not persuasive. Though Wallach et al. did not prepare a fusion multimer and specify the sequences of the TNF monomers or the linker peptides, Wallach et al. did teach that the multimer may be produced by recombinant technologies, and provides ample guidance in Example 4 that such methods were known and practiced by one of ordinary skill in the art.

Applicants' further argue that Wallach et al. teach at column 4, lines 29-31, that "the nature of the amino acids which link the monomers in the recombinantly produced multimer is not critical", and assert that the linker is critical for function of Applicants' claimed receptor molecule. Applicants' also assert that Wallach et al. do not teach that their receptor molecule is capable of binding to a TNF trimer in a stoichiometric ration of 1:1.

Applicants' arguments have been considered but are not persuasive. Wallach et al. stated that the nature of the amino acids which link the monomers in the recombinantly produced multimer is not critical. However, at column 4, lines 19-21, Wallach et al also stated "Those of ordinary skill in the art will be able to determine the optimum length of any such linker molecules to produce multimers which best bind to the TNF trimer." And at lines 31-33,

Wallach et al state that "the optimum length of such linkers in such recombinantly produced proteins can also be determined by routine experimentation." From these statements, it can be reasonably interpreted by the skilled artisan that Wallach et al. teaches that the particular amino acids in the linker are not critical, but that the length for optimum activity is important and can be determined experimentally by one of ordinary skill in the art. The claimed invention would have been *prima facie* obvious as a whole at the time it was made, including maximizing the length of the linker to achieve optimum binding activity, of which a stoichiometric ratio of 1:1 is an inherent feature of maximum binding. In addition, though Applicants' assert in the amendment on page 8 that a concentration of 20pg/ml Hu p75 TNF-R ECD dimer is sufficient to inhibit by 50% the killing activity of 63.5 pg of human TNF, in comparison to 57 pg of the dimeric Hu p75 TNF-R ECD in an Ig backbone which was needed to obtain the same level of protection, and therefore Applicants' receptor is capable of binding to the TNF homotrimer in a stoichiometric ratio of almost 1:1, there is no evidence that the IG fusion receptor does not also bind in a 1:1 ratio. The Ig fusion receptor is significantly larger than Applicants' receptor, and there is no conversion to show what the binding ratio is for the Ig fusion receptor. Therefore, the rejection under 35 USC § 103 is maintained.

It is noted that the previous Examiner indicated that claim 14 was allowable but objected to for depending from a rejected base claim. Though full faith and credit is given to the search and action of a previous examiner, in this particular case it is this Examiner's finding that the nucleotide sequence shown in SEQ ID NO: 1 encoding the chimeric receptor of SEQ ID NO: 2 is obvious over the prior art, since one of ordinary skill in the art would have been able to design a nucleic acid molecule encoding such a receptor from the knowledge of the structure of the

extracellular domains, and through routine experimentation to determine a linker that would provide maximum binding activity.

7.2 Claims 1-3, 6, 8, 14-17 and 19-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al., PN 5,395,760, March 7, 1995.

Claims 1-3, 6, 8, 14-17 and 19-37 encompass receptor molecules which bind to tumor necrosis factor comprising all or a functional portion of two or three extracellular domains of tumor necrosis factor receptors linked via polypeptide linker(s), nucleic acids encoding them, and methods of treatment.

Smith et al. disclose a p75 TNFR (Fig. 2A), and teach at column 10, lines 33-39:

"Both monovalent forms and polyvalent forms of TNF-R are useful in the compositions and methods of the invention. Polyvalent forms possess multiple TNF-R binding sites for TNF ligand. For example, a bivalent soluble TNF-R may consist of two tandem repeats of amino acids 1-235 of Fig. 2A, separated by a linker region."

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to make a dimeric or polyvalent TNF receptor comprising the extracellular domains of TNF-R and linked by a linker or linkers, in order to use such receptors to treat diseases by binding TNF, as suggested by Smith et al. One would have been motivated to do so, because of the number of different diseases found to be associated with TNF, and would have a reasonable expectation of success, since production of chimeric proteins was routine in the art at the time of the invention and since TNF-R Ig fusion proteins were known to be effective for treatment.

It is believed that all pertinent arguments have been answered.

Conclusion

8. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (703) 308-3312. The examiner can normally be reached on Monday through Friday from 9:00 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242.

Informal papers filed by fax should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Eileen B. O'Hara, Ph.D.

Patent Examiner

LORRAINE SPECTOR
PRIMARY EXAMINER